MULTI-VESSEL CORONARY DISEASE AND PERCUTANEOUS CORONARY INTERVENTION

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The goal of percutaneous coronary intervention (PCI) is to provide a safe, effective, less invasive alternative to coronary artery bypass graft surgery (CABG). When introduced by Andreas Gruentzig 25 years ago, he envisioned the procedure to be a technique that would delay the need for CABG until severe multi-vessel coronary disease was present. Over the years, technological advances in equipment and devices have improved safety as well as short and long term outcomes. This has greatly expanded the indications for the technique and allowed more arteries to be accessible to effective treatment with better patient outcomes. In addition, developments in adjuvant pharmacotherapy have further improved outcomes of percutaneous procedures. The results of many large trials in the 1990s have shown that percutaneous intervention can be equally successful when compared to the ''gold standard'' CABG for patients with multi-vessel coronary artery disease. Now with advances in coronary stent technology, including drug eluting stents, multi-vessel angioplasty is set to make another leap forward with further expansion of the indications and improved outcomes.

Approximately two thirds of patients who require revascularisation have multi-vessel disease and two thirds of these have anatomy that is amenable to treatment by percutaneous or open heart procedures.[1] Both techniques have been shown to be relatively safe and highly effective in relieving angina, and have similar mortality and myocardial infarction rates; however, all the major studies have shown fewer additional revascularisation procedures in patients who undergo open heart surgery.[1] It is widely anticipated that the gap in repeat procedures may begin to close with the advent of drug eluting stents.

CONSIDERATIONS IN CHOOSING PCI

When approaching a patient with multi-vessel coronary artery disease there are many factors that should be considered. First, these patients have a less favourable long term outcome; they have increased procedural risk, and increased procedural complexity.[2] They are more likely to have multiple risk factors including diabetes, other co-morbidities, and prior myocardial infarctions with reduced ventricular function. The procedural complexity for percutaneous procedures is increased when unfavourable anatomy such as chronic total occlusions, calcified bifurcation lesions, and diffusely diseased small vessels is present. Unfavourable anatomy is the most common reason for not performing PCI, and the most common anatomical abnormality is a chronic total occlusion occurring in 50% of patients turned down for PCI.[3] The decision to choose PCI as a revascularisation strategy should be based not only on *whether* it can be done safely and successfully, based on the coronary anatomy, but that it *should* be done based on the morbidity and risk when compared to the alternative of medical or surgical treatment.

PRE-STENT STUDIES

Many large randomised studies were undertaken in the 1990s comparing surgical versus percutaneous revascularisation for multi-vessel coronary artery disease. These studies were all done before current percutaneous techniques were available such as coronary stents and glycoprotein inhibitors. Thus conclusions from these trials are limited. Nevertheless they do provide valuable information about the natural history of percutaneous multi-vessel intervention.

Nine randomised clinical trials have compared balloon angioplasty with CABG (fig 1). None except the BARI trial were appropriately sized to assess mortality. However, none has shown a difference in mortality and a meta-analysis of these studies has shown no difference in mortality or recurrent myocardial infarction, with follow up ranging from 1–8 years.[4] All studies have shown that PCI has been associated with a higher rate of repeat revascularisation ranging from 20–40% over the first year, largely due to restenosis. Both techniques have been shown to be highly effective in relieving angina, and by five years no differences in angina relief between the treatment strategies could be seen. Follow up data of patients who where enrolled in the BARI[5] and EAST[6] trials have shown that survival was virtually identical for non-diabetic patients. An economic substudy of the BARI trial showed a small but significant cost saving of PCI over

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Trial	Mortality CABG %	PTCA %	RR
BARI	10.2	10.0	
CABRI	5.7	6.7	
RITA	6.2	6.7	
EAST	18.4	13.7	
GABI	10.2	5.5	
Toulouse	7.9	7.9	
MASS	1.4	6.9	
Lausanne	3.0	8.8	
ERACI	10.0	12.7	

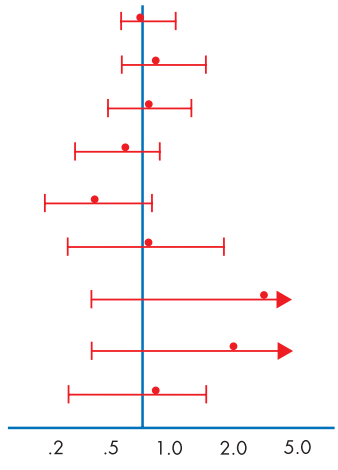

Figure 1 The nine large randomised trials of balloon angioplasty (PTCA) (pre-stent) versus bypass surgery (CABG). The mortality relative risk and confidence intervals are shown.

CABG.[7] The most important finding of the BARI trial was a survival benefit of CABG over coronary angioplasty (PTCA) in the predefined subgroup of treated diabetic patient (fig 2). This was evident, however, only in treated diabetic patients who underwent surgical revascularisation with an internal mammary artery; and the benefit appeared to be due to a reduced mortality when these patients had a subsequent myocardial infarction during follow up[8] (fig 3). Subgroup analysis of diabetic patients treated with only saphenous vein grafts showed no difference in outcome to those who received a balloon angioplasty. The greatest difference was seen in diabetics treated with insulin, while diabetics not on any drug treatment showed no difference in mortality. While these differences were striking for diabetic patients, there was no significant difference among other high risk subgroups, such as patients with triple vessel disease, left anterior descending disease, left ventricular dysfunction, or those with type C lesions. In particular, in non-diabetic patients, PTCA and CAGB were more equivalent to the CABG group in subgroups known to have a substantial advantage over medical treatment such as three vessel disease and poor left ventricular function.

While the BARI trial results in treated diabetic patients led to an initial recommendation that they should undergo CABG, analysis of the registry portion of the study did not support this conclusion.[9] It was found that, not surprisingly, patients with more severe disease underwent CABG while those with less severe disease received angioplasty. When the outcomes of the two treatments were compared there was no difference in long term outcome. The investigators concluded that angioplasty was a safe alternative to CABG in diabetic patients when they are properly selected.

One of the criticisms of the BARI study's conclusions about diabetics is that all the study patients were not treated with modern secondary prevention care, such as cholesterol reduction, angiotensin converting enzyme (ACE) inhibition, and glycaemic control. The average low density lipoprotein (LDL) cholesterol concentration of the diabetics over the first five years of the study went from 143 to 141 mg/dl. In light of studies such as CARE, 4S, and LIPID, decreasing LDL aggressively decreases coronary events by 19–55%.[10] Likewise only 20% of patients were on ACE inhibitors and, given the results of several trials including the HOPE trial, long term outcome would be expected to improve with such treatment.[11] In addition, glycaemic control was not measured and optimal control was not mandated. In view of the data showing improved outcomes with optimal glycaemic control, it is likely that the BARI trial would have shown improved outcomes if glycaemic control and these risk factors had been aggressively addressed.[12] Accordingly the BARI 2D study is currently underway to evaluate an early revascularisation strategy or medical treatment and insulin providing or insulin sparing strategy in asymptomatic or mildly symptomatic patients with treated diabetes and significant coronary artery disease.[13] Optimal management of glycaemia and risk factors is required for all patients.

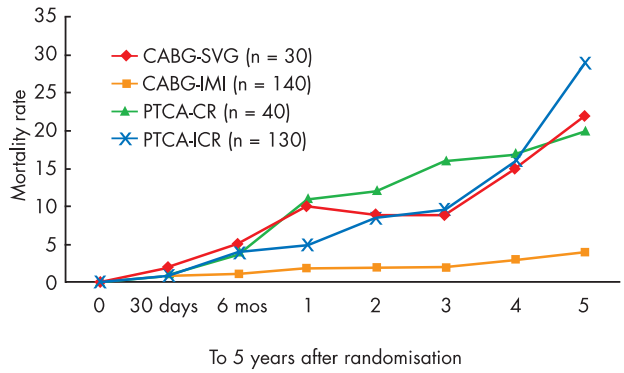

Figure 2 Graphs illustrating how mortality in treated diabetics was improved over balloon angioplasty only if they received an internal mammary artery graft (CABG-IMI).

POST-STENT STUDIES

Four recent studies comparing CABG with stents in patients with multi-vessel disease have shown similar mortality overall (fig 4) and similar myocardial infarction rates (fig 5). All have shown a better acute and long term outcome for percutaneous intervention at a decreased cost, but repeat revascularisation procedures were still significantly greater than in those undergoing CABG. The ARTS trial compared coronary artery bypass surgery and multi-vessel stenting.[14] At one year follow up, there was no significant difference between the groups in terms of mortality, stroke, or myocardial infarction rates in 1205 randomised patients. Of the patients who did not have a myocardial infarction or stroke, 16.8% in the stenting group and 3.5% in the surgical group underwent subsequent revascularisation. Also, diabetes was a predictor of worse outcome with either strategy, as it was in the BARI trial. The mortality of the diabetic group was higher in the stent group but this did not reach significance. A carefully undertaken economic substudy showed a cost saving for the stented group of $2000 at one year.

ERACI-II was similar to the ARTS trial. In this study, 405 patients were randomised to either multi-vessel angioplasty with stents or to surgical revascularisation.[15] The primary end point was a major adverse cardiac event, including death, myocardial infarction or stroke at 30 days. At an average of 18 months follow up the survival for the stented group was 96.9% versus 92.5% for the patients randomised to surgery ($p < 0.017$). However, as in previous trials, revascularisation rates were higher in the stented group.

The MASS II trial randomised patients to medical treatment (n = 203), PCI (n = 205), or CABG (n = 203).[16] Seventy per cent of the PCI patients received stents. There was no difference in mortality at one year, but subsequent revascularisation was highest in the medical group (11%) and no different for the PCI group (9%), while the surgical group had only a 1% incidence of revascularisation. As would be expected the greatest angina relief occurred with both revascularisation strategies.

The SOS trial randomised 480 patients to PCI and stenting and 481 to CABG.[17] Surprisingly the mortality was higher in the PCI group (4%) than in the CABG group (1%). As in the previous trials the incidence of repeat revascularisation was significantly more for the PCI group than the surgical group (20% *v* 5%).

While these more current studies using stents did not show qualitative differences from the earlier studies, the rate of complications, in particular, the incidence of repeat revascularisation, was significantly lower. On average the incidence of repeat revascularisation, largely caused by restenosis, was 45% in the pre-stent era and 20% in the post-stent era.

While there have been significant advances in PCI, there have also been advances in surgery. One of the observations from earlier studies of CABG has been the decline in cognitive function that occurs following coronary pulmonary bypass. A meta-analysis of 23 studies of post-CABG patients found a 22.5% rate of cognitive impairment at two months.[18] In another study 20% of CABG patients had a decline in verbal and visual memory that persisted for one year postoperatively.[19] Current techniques including off-pump surgery appear to reduce this problem, as well as reduce morbidity and duration of hospitalisation.

SINGLE SETTING AND STAGED PROCEDURES

In the initial use of angioplasty, interventions were routinely performed at a later time after the diagnostic angiogram. This was in an effort to reduce complications such as contrast induced renal failure. Also, the imaging quality was not adequate to carefully evaluate the lesions and plan the interventional strategy. Currently, however, it has become common to perform an intervention at the same session as the diagnostic angiogram, even in the setting of multi-vessel angioplasty. Data from the National Heart, Lung, and Blood Institute PTCA dynamic registry from 1999–2001 show that 30% of patients are treated in a single session. Registry data from the period 1992-95 revealed that the risk of complications where twofold greater for single setting multi-vessel angioplasty versus a delayed procedure.[20] However, this was before widespread stent use was available, when acute closure was a major problem. Now with intracoronary stents,

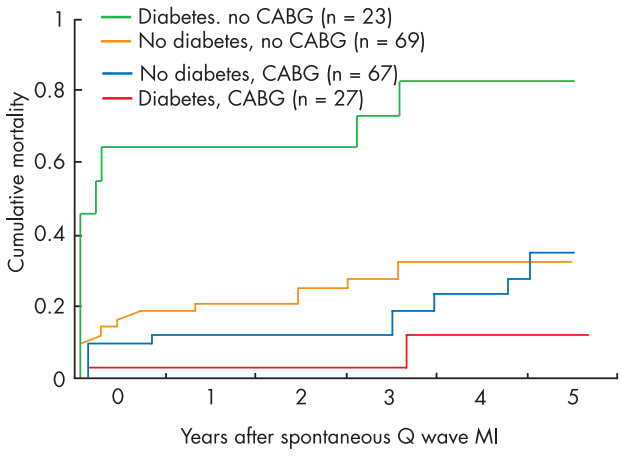

Figure 3 The increased mortality in diabetic patients receiving balloon angioplasty is predominantly caused by Q wave myocardial infarction.

Trial acronyms

ARTS: Arterial Revascularization Therapies Study
ASPECT: Asian Paclitaxel Eluting Stent Clinical Trial
BARI: Bypass Angioplasty Revascularization Investigation
CARE: Cholesterol And Recurrent Events
CREDO: Clopidogrel for Reduction of Events During Observation
CURE: Clopidogrel in Unstable angina to prevent Recurrent Events
EAST: Emory Angioplasty versus Surgery Trial
ELUDES: European Evaluation of Paclitaxel Eluting Stent
EPISTENT: Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
HOPE: Heart Outcomes Prevention Evaluation
LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease
MASS: Medical, Angioplasty and Surgery Study
RAVEL: Randomized Study with the Sirolimus Eluting Velocity Balloon Expandable Stent
4S: Scandinavian Simvastatin Survival Study
SOS: Stent Or Surgery
TAXUS: Taxus Paclitaxel Eluting Stent for the Reduction of Restenosis after Angioplasty and Stenting

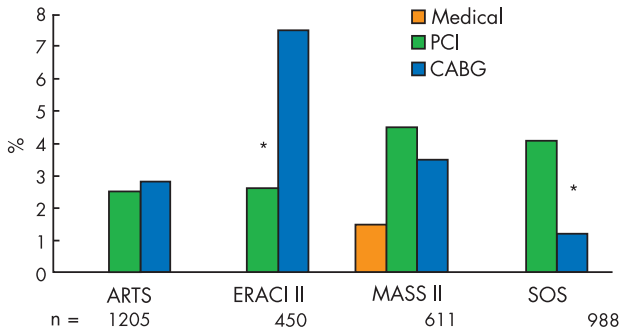

Figure 4 The four major trials of stents (PCI) versus CABG for multi-vessel disease show similar mortality overall. *Significantly different.

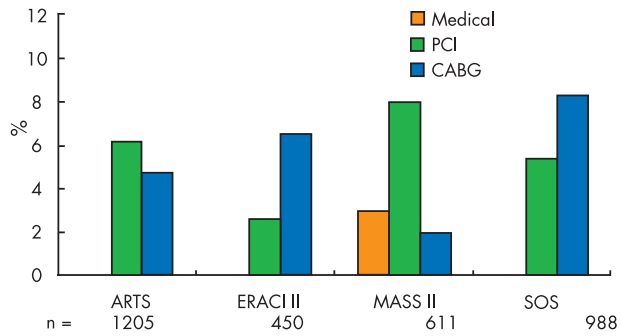

Figure 5 The four major trials of stents (PCI) versus CABG for multi-vessel disease show similar myocardial infarction rates overall.

the interventionalist is able to confidently treat a multitude of high risk and difficult lesions without significant worry of acute closure. The situations that can favour planned or unplanned staged procedures include the desire to reduce the risk of the procedure, avoid excessive contrast use, reduce patient discomfort, and physician fatigue.

COMPLETE VERSUS INCOMPLETE REVASCULARISATION

Although complete revascularisation is the goal in most patients undergoing multi-vessel intervention, incomplete revascularisation is common in clinical practice. In the BARI trial, five year survival was not different between the two groups, even though 91% of important lesions were bypassed while only 51% of important lesions were successfully dilated. In the angioplasty group, five year rates of death, cardiac death, repeat revascularisation, and angina were similar in patients treated with intended incomplete revascularisation as compared to when complete revascularisation was the intended strategy.[21] In those patients in whom complete percutaneous revascularisation was intended, only half of the target lesions where attempted and successfully dilated. Except in diabetic patients, incomplete revascularisation did not impact long term survival. Also, repeat revascularisation procedures were mostly for restenosis, rather than revascularisation of previously untreated lesions.

Many patients can be considered for incomplete but still adequate revascularisation. Patients with clearly identifiable lesions, which are favourable for intervention and serve a large territory, should be considered for revascularisation. In this strategy, lesions in small or diffusely diseased vessels and lesions serving infarcted territories may be safely left alone. If the patient continues to have angina or a subsequent stress test shows ischaemia in that territory, a second procedure can be performed to revascularise the vessel that was previously not attempted.

ADJUNCTIVE TREATMENT

Adjunctive medicines peri- and post-procedure have improved long term outcomes after percutaneous interventions. Glycoprotein IIb/IIIa agents have been shown to reduce complications in both low and high risk patients through a reduction in non-Q wave myocardial infarction.[22] These often small enzyme leaks have been shown to be associated with a poor long term outcome. The mechanism is not known for this adverse outcome but it has been speculated that it is related to the extent of disease, a decrease in microvascular flow, side branch occlusion, and increased inflammatory markers. The EPISTENT trial compared balloon angioplasty with abciximab, stenting with placebo, and stenting with abciximab in diabetics and non-diabetics.[23] The composite end point of death, myocardial infarction, or target vessel revascularisation was significantly decreased with both stenting and abciximab in the diabetic group (23.4% *v* 13.0%, p = 0.006). The mortality rate of the non-diabetics in both groups was toward better outcomes with stents and abciximab, although this trend was not significant. A meta-analysis of all glycoprotein IIb/IIIa trials in PCI has shown an average decrease in major adverse cardiac events of 10%.[22]

The PCI-CURE trial assessed pre-and nine months post-treatment with clopidogrel on PCI outcomes when used for unstable angina.[24] The composite end point of death or myocardial infarction was significantly less in the long term clopidogrel group (8.8% *v* 12.6%, p = 0.02). The recent CREDO trial further supports prolonged use of clopidogrel for up to one year following stent placement in both stable and unstable angina. Current recommendations are for prolonged use of clopidogrel in all patients with unstable angina undergoing PCI or treated with medical treatment, but to discontinue it five days before CABG.

Antithrombotic agents such as the low molecular weight heparin enoxaparin have also been shown to improve outcomes in patients with acute coronary syndromes.[25] Evidence is also emerging that these agents may be advantageous in patients undergoing PCI. Newer agents such as pentasaccarides and anti-Xa agents may further improve management.

RESTENOSIS, RADIATION, AND DRUG ELUTING STENTS

Restenosis has remained one of the main limitations of coronary angioplasty since its introduction 25 years ago. While stents have reduced the problem by 50% through prevention of remodelling, restenosis continues to be a significant problem particularly for patients with multi-vessel disease. Lesion length, vessel size, total occlusion, and number of lesions all increase the incidence of restenosis. While pharmacologic trials have been remarkably unsuccessful, two new techniques have proven to be effective.

Intravascular radiation therapy in six randomised trials has been shown to be effective in reducing in-stent restenosis by 50%.[26] This reduction is seen in untouchable anatomy as well as long lesions, small vessels, and saphenous vein grafts; importantly it is also effective in diabetics. Unfortunately the studies of radiation in de novo lesions with or without stents have not been shown to be effective and it is not currently

indicated for this use. A number of problems have become apparent with radiation, including edge restenosis caused by geographical miss and/or inadequate dose, and late stent thrombosis, that all can lead to late adverse events. With careful placement of the radiation to adequately cover the lesion with a margin of at least 5 mm at either end, use of at least a 14 Gy dose, and prolonged use of clopidogrel, these complications have been minimised.

While radiation can reduce in-stent restenosis, the greater problem of preventing restenosis has been extremely difficult to resolve. This has been because of a poor understanding of the pathophysiology of restenosis and an inability to deliver adequate dosage of drugs to the injured arterial site. Drug eluting stents offer some theoretical advantages in that they can deliver high dosages of drugs not possible with systemic administration and can deliver it directly to the injured vessel. The most promising drug eluting stents have produced dramatic decreases in restenosis rates (fig 6). A large number of drug eluting stents are undergoing clinical investigation currently, but two drugs have shown the greatest promise—rapamycin (sirolimus) and paclitaxel.[27]

Rapamycin is a macrolide antibiotic used in transplantation for its anti-inflammatory and antiproliferative actions. The first randomised clinical trial of 258 patients is the RAVEL trial which showed dramatic results with a restenosis rate of 0% as compared to the bare stent rate of 26%.[28] These results have been confirmed by the SIRIUS trial of 1104 patients where the restenosis rate was 9% as compared to 32%.[29] The Canadian C-SIRIUS trial in long lesions in smaller vessels confirmed their findings. This has led to their approval in Europe and USA.

Paclitaxel is a microtubule inhibitor that also has antiprolifertive effects. The TAXUS, ELUDES, and ASPECT trials all showed similarly low restenosis rates of 0–4%. A larger trial (TAXUS IV) with this agent is still ongoing.

While these studies have been positive use of other agents have not been, raising concerns about both the importance of the stent platform for drug delivery and the drug itself. The drug may be the most important factor in the stent's success. Several small studies of oral rapamycin have shown promising results and have raised the possibility of combination therapy.[30] Cost issues are significant and long term outcome still needs to be defined. In addition these devises have not been carefully studied in patients with multi-vessel disease and unfavourable anatomy. These studies are necessary before we can be assured that the problem of restenosis has been adequately controlled and we can expect outcomes similar to CABG in patients with multi-vessel disease.

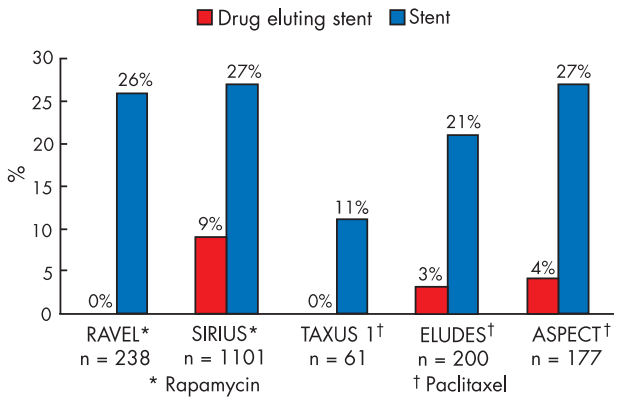

Figure 6 Graphs showing the results of the rapamycin and paclitaxel eluting stent trials and the dramatic reduction in restenosis in single vessel disease.

CONCLUSIONS

Patients with multi-vessel disease comprise the majority of patients undergoing PCI today and will likely remain so. With improved techniques, stents, and adjunctive drugs, outcomes have improved significantly. It is anticipated that if the early experience with drug eluting stents is replicated in multi-vessel disease then the outcomes of PCI will be equivalent to CABG. PCI would therefore become a preferred strategy for the majority of patients needing revascularisation. Initial estimates suggest that the number of PCI procedures will grow by 10% while surgical cases will fall. The decline in restenosis will be equally offset by increased percutaneous revascularisation. The future is clearly bright for angioplasty and the advances over the past 25 years have been truly remarkable.

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